HEPATITIS C
Jan-Feb 2005

1: ACP J Club. 2005 Jan-Feb;142(1):A12; author reply A13.
Comment on:
ACP J Club. 2005 Jan-Feb;142(1):10-1.
Peginterferon alpha-2a improved the hepatitis C virologic response in concurrent HIV and chronic hepatitis C virus infections.
Torriani FJ, Chung RT.
Publication Types:
Comment
Letter
PMID: 15656540 [PubMed - indexed for MEDLINE]

2: Am J Gastroenterol. 2004 Dec;99(12):2359-64.
A pilot study of interleukin-11 in subjects with chronic hepatitis C and advanced liver disease nonresponsive to antiviral therapy.
Lawitz EJ, Hepburn MJ, Casey TJ.
Gastroenterology Service, Brooke Army Medical Center, San Antonio, Texas, USA.
OBJECTIVES: To evaluate the effects of recombinant human interleukin (rhIL)-11 on liver histology in patients with chronic hepatitis C virus (HCV) infection and advanced liver disease who had failed antiviral therapy. METHODS: This was an open-label study of rhIL-11 (Neumega), Wyeth Laboratories, Collegeville, PA) at a dose of 5 microg/kg administered by subcutaneous injection daily for 12 wk. The primary efficacy endpoint was the change in the Knodell Histology Activity Index (HAI) between pre- and posttreatment liver biopsies. Secondary efficacy endpoints included changes in plasma alanine transaminase (ALT) concentrations and in the number of platelets. RESULTS: The Knodell HAI improved in 11 (55%) of the 20 subjects enrolled, with the mean score improving from 7.3 to 5.9 (p= 0.006). Eight subjects (40%) experienced significant improvement as defined by a decrease of at least two points in the HAI. IL-11 treatment was also associated with a decrease in ALT levels from a mean level of 113 IU/L at baseline to 65 IU/L at week 12 (p < 0.001). Platelet levels increased from a mean of 143 x 10(3)/microl at baseline to 198 x 10(3)/mul at week 12 of treatment (p < 0.001).
Overall, rhIL-11 was well tolerated and no serious adverse events (AEs) were reported. The most common AE was edema of the lower extremities, which occurred in all subjects. CONCLUSIONS: The findings from this pilot study suggest that rhIL-11 may be beneficial for patients with hepatic inflammation and advanced liver disease associated with chronic HCV infection. Larger clinical trials are warranted to further evaluate the long-term antiinflammatory and antifibrotic effects of rhIL-11.
PMID: 15571583 [PubMed - indexed for MEDLINE]

3: Am J Hematol. 2004 Dec;77(4):419-20.

Rituximab is effective for human herpesvirus-8-negative primary effusion lymphoma with CD20 phenotype associated hepatitis C virus-related liver cirrhosis.
Takao T, Kobayashi Y, Kuroda J, Omoto A, Nishimura T, Kamitsuji Y, Fukiya E, Nakamura C, Kimura S, Yoshikawa T.
Publication Types:
Case Reports
Letter
PMID: 15551361 [PubMed - indexed for MEDLINE]

4: Am J Hematol. 2004 Dec;77(4):421.
Prevalence of hepatitis C virus infection in IgM-type monoclonal gammopathy of uncertain significance and Waldenstrom macroglobulinemia.
Veneri D, Aqel H, Franchini M, Meneghini V, Krampera M.
Publication Types:
Letter
PMID: 15551289 [PubMed - indexed for MEDLINE]

5: Am J Infect Control. 2004 Dec;32(8):493-5.
Hepatitis B and hepatitis C virus prevalence among dialysis patients in Bahrain and Saudi Arabia: a survey by serologic and molecular methods.
Qadi AA, Tamim H, Ameen G, Bu-Ali A, Al-Arrayed S, Fawaz NA, Almawi WY.
College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Bahrain.
Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections were assessed among 81 Bahraini and 34 Saudi hemodialysis patients and 7714 Bahraini and 2330 Saudi blood donors. Higher prevalence of HCV (9.24% vs 0.30%), hepatitis B surface antigen (5.88% vs 0.62%) were seen in patients versus control patients, and in Saudi patients compared with Bahraini patients. HCV genotypes were HCV 1a/1b plus HCV 4 among Bahraini patients and HCV 2/2a plus HCV 4 among Saudi patients. This is the first report on viral hepatitis in Bahrain and the first to compare HBV/HCV among dialysis patients in the Eastern Arabian Peninsula.
PMID: 15573057 [PubMed - indexed for MEDLINE]

6: Am J Psychiatry. 2004 Dec;161(12):2332; author reply 2332-4.
Comment on:
Am J Psychiatry. 2004 Mar;161(3):429-35.
Interferon for hepatitis C patients with psychiatric disorders.
Wilson MS 2nd.
Publication Types:
Comment
Letter
PMID: 15569921 [PubMed - indexed for MEDLINE]

7: Am J Psychiatry. 2004 Dec;161(12):2332; author reply 2332-4.
Comment on:
Am J Psychiatry. 2004 Mar;161(3):429-35.
Interferon for hepatitis C patients with psychiatric disorders.
Asnis GM, De La Garza R, Rego SA, Henderson MA, Reinus JF.
Publication Types:
Comment
Letter
PMID: 15569920 [PubMed - indexed for MEDLINE]

8: Am J Psychiatry. 2004 Dec;161(12):2331-2; author reply 2332-4.
Comment on:
Am J Psychiatry. 2004 Mar;161(3):429-35.

Interferon for hepatitis C patients with psychiatric disorders.
Rifai MA, Bozorg B, Rosenstein DL.
Publication Types:
Comment
Letter
PMID: 15569919 [PubMed - indexed for MEDLINE]

9: Ann Intern Med. 2005 Jan 18;142(2):105-14.
Comment in:
Ann Intern Med. 2005 Jan 18;142(2):I51.
Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival.
Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, Arakawa Y, Hashimoto E, Hirota K, Yoshida H, Ohashi Y, Omata M; Tokyo-Chiba Hepatitis Research Group.
University of Tokyo, Japanese Red Cross Medical Center, Nippon University School of Medicine, and Tokyo Women's Medical College. shirato@cc.okayama-u.ac.jp <shirato@cc.okayama-u.ac.jp>
BACKGROUND: Although cirrhosis is a major risk factor for development of hepatocellular carcinoma, no definitive prospective analyses have assessed the long-term efficacy of antiviral therapy in cirrhotic patients. OBJECTIVE: To elucidate the role of antiviral therapy in the suppression of liver tumors and survival over a long-term follow-up period. DESIGN: Prospective cohort study. SETTING: 25 clinical centers. PATIENTS: 345 patients with chronic hepatitis C and cirrhosis enrolled in previous trials. INTERVENTION: 271 patients received 6 to 9 million U of interferon 3 times weekly for 26 to 88 weeks; 74 received no treatment. MEASUREMENTS: Blood tests and abdominal ultrasonography were done regularly to detect hepatocellular carcinoma. RESULTS: Hepatocellular carcinoma was detected in 119 patients during a 6.8-year follow-up: 84 (31%) in the interferon-treated group and 35 (47%) in the untreated group. Cumulative incidence of hepatocellular carcinoma among interferon-treated patients was significantly lower than in untreated patients (Cox model: age-adjusted hazard ratio, 0.65 [95% CI, 0.43 to 0.97]; P = 0.03), especially sustained virologic responders. A total of 69 patients died during follow-up: 45 (17%) in the treated group and 24 (32%) in the untreated group. Interferon-treated patients had a better chance of survival than the untreated group (Cox model: age-adjusted hazard ratio, 0.54 [CI, 0.33 to 0.89]; P = 0.02). This was especially evident in sustained virologic responders. LIMITATION: This was not a randomized, controlled study. Patients enrolled in the control group had declined to receive interferon treatment even though they were eligible for treatment. CONCLUSION: Interferon therapy for cirrhotic patients with chronic hepatitis C, especially those in whom the infection had been cured, inhibited the development of hepatocellular carcinoma and improved survival.
Publication Types:
Clinical Trial
PMID: 15657158 [PubMed - indexed for MEDLINE]

10: Ann Intern Med. 2005 Jan 18;142(2):I53.
Wide range of drugs now available to effectively treat chronic heart failure.
[No authors listed]
PMID: 15657154 [PubMed - indexed for MEDLINE]

11: Ann Intern Med. 2005 Jan 18;142(2):I51.

Comment on:
Ann Intern Med. 2005 Jan 18;142(2):105-14.
Summaries for patients. Long-term effects of antiviral treatment for hepatitis C. [No authors listed]

Publication Types:
Comment
Patient Education Handout
PMID: 15657153 [PubMed - indexed for MEDLINE]

12: Br J Ophthalmol. 2004 Dec;88(12):1518-20.
Is screening for interferon retinopathy in hepatitis C justified?
Cuthbertson FM, Davies M, McKibbin M.
St James University Hospital, Beckett Street, Leeds LS9 7TF, UK.
fcuthbertson@hotmail.com
BACKGROUND/AIM: In the treatment of hepatitis C, the National Institute for Clinical Excellence advocates use of a combination of interferon alfa and ribavirin for selected patients. Retinopathy is a well recognised side effect of interferon therapy and is characterised by retinal haemorrhages, cotton wool spots, and macular oedema. The aim of this study was to document the incidence and natural history of the retinopathy in patients treated with a long acting (pegylated) interferon and ribavirin for hepatitis C and to assess the need to screen for retinal complications. METHODS: All patients started on treatment from September 2002 to August 2003 were invited to participate in the study. The past medical and ocular history, visual symptoms, and the results of a full ophthalmological assessment performed 3 months after starting treatment were noted. Any patient with retinal changes was followed up at 3 month intervals until the changes resolved. RESULTS: Of the 25 patients examined, four had evidence of retinopathy including deep retinal haemorrhage and cotton wool spots. Two of the patients were diabetic and one hypertensive. None had any visual symptoms and in all four the retinopathy resolved while the patients completed their course of treatment. CONCLUSIONS: The incidence of retinopathy with pegylated interferon is low. The retinal complications resolve while treatment is continued and are asymptomatic. This study does not support routine screening for retinopathy in patients treated with pegylated interferon and ribavirin for hepatitis C.
PMID: 15548803 [PubMed - indexed for MEDLINE]

13: Clin Microbiol Infect. 2004 Dec;10(12):1075-80.
Qualitative multiplex RT-PCR for simultaneous detection of hepatitis C virus and human immunodeficiency virus in plasma samples.
Adami V, Falasca E, Dorotea L, Malangone W, Astori G, Marini L, Biffoni F, Rinaldi C, Degrassi A, Pipan C.
Consorzio Fenice, DRMM University of Undine, Udine, Italy.
This report describes the development of a one-tube multiplex reverse transcriptase (RT)-PCR assay for the simultaneous detection of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) in plasma samples. The assay was evaluated with two panels of HCV- and HIV-1-positive samples, as well as negative plasma specimens. Extraction and amplification of HCV and HIV-1 RNA from plasma samples were performed in a single reaction, and amplified genomes were detected with specific probes. Serial dilutions of the HCV and HIV-1 first World Health Organization International Standards were used to evaluate the sensitivity of the method. Two RNA controls were constructed to determine inter-assay variations and the sensitivity of the amplification step. The assay had good specificity and detected all the genotypes and subtypes tested. The

analytical sensitivity of the entire assay was 100 IU/mL for HCV and 200 IU/mL for HIV-1, while the amplification step detected ten copies/reaction for HCV and 20 copies/reaction for HIV-1. The multiplex assay allowed the simultaneous extraction, amplification and detection of two virus genomes, thereby providing an important practical advantage and an efficient approach for analysing individual and pooled plasma donations.
Publication Types:
Validation Studies
PMID: 15606634 [PubMed - indexed for MEDLINE]

14: Clin Microbiol Infect. 2004 Dec;10(12):1067-74.
Modifications of haematological series in patients co-infected with human immunodeficiency virus and hepatitis C virus during treatment with interferon and ribavirin: differences between pegylated and standard interferon.
Arizcorreta A, Brun F, Fernandez-Gutierrez C, Garcia Juarez R, Guerrero F, Perez-Guzman E, Giron-Gonzalez JA.
Internal Medicine, Hospital Universitario Puerta del Mar, Facultad de Medicina, Cadiz, Spain.
Therapy with interferon and ribavirin for hepatitis C virus (HCV) infection induces a decrease in several haematological population counts. It is unclear whether haematological toxicity is more severe in patients co-infected with HCV and human immunodeficiency virus (HIV). This study analysed the evolution of haematological population counts during and after interferon and ribavirin therapy for chronic HCV infection. Eleven patients co-infected with HIV and HCV and treated with pegylated interferon plus ribavirin, and ten treated with standard interferon plus ribavirin, were analysed. With reference to baseline values, neutrophil counts decreased by an average of 45% (range 18-67%), total lymphocytes by 50% (16-63%), CD4 lymphocytes by 54% (16-61%), haemoglobin by 9%
(5-16%) and platelets by 31% (16-45%). The nadir of the decrease was reached in the first weeks of therapy and was maintained while patients were receiving treatment. The reduction in all series was higher with pegylated interferon. Patients recovered their baseline counts after finishing the treatment. No cases of haemorrhage or outstanding infection were detected during follow-up.
Publication Types:
Clinical Trial
Controlled Clinical Trial
PMID: 15606633 [PubMed - indexed for MEDLINE]

15: Clin Pharmacol Ther. 2005 Jan;77(1):90-100.
Neurocognitive changes in patients with hepatitis C receiving interferon alfa-2b and ribavirin.
Kraus MR, Schafer A, Wissmann S, Reimer P, Scheurlen M.
Department of Gastroenterology and hepatology, Medizinische Poliklinik, University of Wurzburg, D-97070 Wurzburg, Germany.
kraus_m@klinik.uni-wuerzburg.de
BACKGROUND: During antiviral therapy of chronic hepatitis C, patients frequently report impairment of concentration or memory. Therefore we prospectively investigated neurocognitive performance in patients receiving interferon alfa and ribavirin. METHODS: Repeated computer-based testing of neurocognitive function was performed in 70 patients with chronic hepatitis C receiving interferon alfa-2b (pegylated or conventional) and ribavirin. In addition, depression scores were obtained (Hospital Anxiety and Depression Scale). RESULTS: Reaction times were significantly increased during treatment (mean reaction time increase after 3 months of therapy: alertness, 46.76 ms [95%

confidence interval (CI)], 26.86-66.66 ms), P < .001; divided attention, 47.04 ms [95% CI, 26.44-67.64 ms], P < .001; vigilance, 60.78 ms [95% CI, 29.24-92.32 ms], P < .001; and working memory, 38.53 ms [95% CI, 1.22-75.83], P = .34). Accuracy measures (number of false reactions) were affected for the working-memory task exclusively. Cognitive performance returned to pretreatment values after the end of therapy. Cognitive impairment was not significantly correlated with the degree of concomitant depression (0.04 < r [absolute value] < 0.10, P > .390). CONCLUSIONS: Interferon-based combination therapy of chronic hepatitis C causes significant but reversible impairment of neurocognitive performance. Consequences for the requirements of an active life in patients with chronic hepatitis C receiving antiviral therapy need to be assessed.
PMID: 15637534 [PubMed - indexed for MEDLINE]

16: Gastroenterology. 2004 Dec;127(6):1724-32.
Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels.
Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, Shiffman M, Farci P, Gitlin N, O'Brien CB, Lamour F, Lardelli P; PEGASYS Study NR16071 Investigator Group.
Saarland University Hospital, Homburg/Saar, Germany.
zeuzem@uniklinik-saarland.de
BACKGROUND & AIMS: Patients with chronic hepatitis C and persistently normal alanine aminotransferase (ALT) levels have been routinely excluded from large randomized treatment trials; consequently, the efficacy and safety of antiviral therapy in this population are unknown. METHODS: Patients with at least 3 normal ALT values over an 18-month period were randomized (3:3:1) to treatment with peginterferon alfa-2a 180 mug/wk plus ribavirin 800 mg/day for 24 weeks (212 patients), the same combination for 48 weeks (210 patients), or no treatment (69 patients) in a multinational study. All patients were monitored for 72 weeks.
The primary measure of efficacy was sustained virologic response (SVR), defined as undetectable serum hepatitis C virus (HCV) RNA by qualitative polymerase chain reaction at the end of 24 weeks of untreated follow-up. RESULTS: No patient cleared HCV RNA in the untreated control group. SVR rates of 30% and 52% were obtained in the 24- and 48-week treatment groups, respectively. In patients infected with HCV genotype 1, SVR rates of 13% and 40% were obtained with 24 and
48 weeks of treatment, respectively (P < .0001). In patients infected with genotypes 2 or 3, SVR rates were 72% and 78% with 24 and 48 weeks of treatment, respectively (P = .452). Treatment-related flares in ALT activity were not observed. CONCLUSIONS: The efficacy and safety of peginterferon alfa-2a and ribavirin combination therapy in patients with chronic hepatitis C and persistently normal ALT levels are similar to that in patients with elevated ALT levels. The indication for treatment of hepatitis C can be evaluated independently from baseline ALT activity.
Publication Types:
Clinical Trial
Multicenter Study
Randomized Controlled Trial
PMID: 15578510 [PubMed - indexed for MEDLINE]

17: Gut. 2005 Feb;54(2):297-302.
Changes to hepatocyte ploidy and binuclearity profiles during human chronic viral hepatitis.

Toyoda H, Bregerie O, Vallet A, Nalpas B, Pivert G, Brechot C, Desdouets C.
Inserm U370-Pasteur Institute, CHU Necker, 156, rue de Vaugirard, 75015, Paris, France.
BACKGROUND AND AIMS: The importance of the hepatocyte ploidisation pattern to the control of cell proliferation and differentiation has been well established. However, there are no data that have characterised hepatocyte ploidy at various stages of chronic liver inflammation and fibrosis in vivo. METHODS: We therefore investigated hepatocyte ploidy/binuclearity patterns in 57 patients with chronic hepatitis, using a recently developed methodology which allows simultaneous hepatocyte ploidy and binuclearity analyses on the same liver section. RESULTS: The percentage of mononuclear diploid hepatocytes was significantly reduced in patients with high hepatitis activity and marked fibrosis (low activity: 75.1 (18.8)% v high activity: 61.8 (21.6)%, p=0.0111, and low fibrosis: 77.3 (13.8)% v high fibrosis: 57.4 (23.3)%, p=0.0002). Accordingly, the percentage of mononuclear polyploid hepatocytes increased in patients with high hepatitis activity and marked fibrosis (low activity: 11.9 (15.5)% v high activity: 22.2 (20.1)%, p=0.0166, and low fibrosis: 9.4 (10.7)% v high fibrosis: 26.4 (21.6)%, p=0.0001). In addition, the fraction of binuclear hepatocytes was significantly higher in patients with hepatitis B virus (HBV) than in those with hepatitis C virus (HCV) infections (HBV: 18.2 (7.6)% v HCV: 12.0 (4.8)%; p=0.0020). Under multivariate analysis, HBV infection was an independent factor accounting for the larger binuclear hepatocyte fraction (p=0.0294). CONCLUSION: Our results revealed an increase in the polyploid hepatocyte fraction which correlates with the severity of chronic hepatitis; moreover, we demonstrated that HBV and HCV related chronic hepatitis exhibited distinctive hepatocyte ploidy patterns, thus allowing the suggestion that these two viral infections may modulate liver ploidy through different mechanisms.
PMID: 15647198 [PubMed - indexed for MEDLINE]

18: Gut. 2005 Jan;54(1):172-3.
Comment on:
Gut. 2003 Oct;52(10):1532.
Antiviral treatment initiation costs in chronic hepatitis C.
Siebert U, Wasem J, Rossol S, Sroczynski G, Aidelsburger P, Ravens-Sieberer U, Kurth BM, Manns MP, McHutchison JG, Wong JB.
Publication Types:
Comment
Letter
PMID: 15591531 [PubMed - indexed for MEDLINE]

19: Gut. 2005 Jan;54(1):128-33.
Hepatic vein transit times using a microbubble agent can predict disease severity non-invasively in patients with hepatitis C.
Lim AK, Taylor-Robinson SD, Patel N, Eckersley RJ, Goldin RD, Hamilton G, Foster GR, Thomas HC, Cosgrove DO, Blomley MJ.

Imaging Sciences Department, MRC Clinical Services Centre, Faculty of Medicine, Imperial College, The Robert Steiner MR Unit, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK. a.lim@ic.co.uk
BACKGROUND AND AIMS: A reliable non-invasive assessment of the severity of diffuse liver disease is much needed. We investigated the utility of hepatic vein transit times (HVTT) for grading and staging diffuse liver disease in a cohort of patients with hepatitis C virus (HCV) infection using an ultrasound microbubble contrast agent as a tracer. MATERIALS AND METHODS: Eighty five untreated patients with biopsy proven HCV induced liver disease were studied

prospectively. All were HCV RNA positive on polymerase chain reaction testing. Based on their histological fibrosis (F) and necroinflammatory (NI) scores, untreated patients were divided into mild hepatitis (F < or =2/6, NI < or =3/18), moderate/severe hepatitis (3 < or =F <6 or NI > or =4), and cirrhosis (F=6/6) groups. In addition, 20 age matched healthy volunteers were studied. After an overnight fast, a bolus of contrast agent (Levovist) was injected into an antecubital vein and spectral Doppler signals were recorded from both the right and middle hepatic veins for analysis. HVTTs were calculated as the time from injection to a sustained rise in Doppler signal >10% above baseline. The Doppler signals from the carotid artery were also measured in 60 patients and carotid delay times (CDT) calculated as the difference between carotid and hepatic vein arrival times. The earliest HVTT in each patient was used for analysis. RESULTS: Mean (SEM) HVTT for the control, mild hepatitis, moderate/severe hepatitis, and cirrhosis groups showed a monotonic decrease of 38.1 (2.8), 38.8 (2.4), 26.0 (2.4), and 15.8 (0.8) seconds, respectively. Mean (SEM) CDT for the control, mild hepatitis, moderate/severe hepatitis, and cirrhosis patients again showed progressive shortening of 30.3 (2.6), 25.9 (2.6), 14.8 (2.1), and 5.6 (1.2) seconds, respectively. There were significant differences between the groups for HVTT (ANOVA, p<0.001) and CDT (ANOVA, p<0.001). There was 100% sensitivity and 80% specificity for diagnosing cirrhosis and 95% sensitivity and 86% specificity for differentiating mild hepatitis from more severe liver disease. CONCLUSION: We have shown, for the first time, that HVTT using an ultrasound microbubble contrast agent can assess HCV related liver disease with clear differentiation between mild hepatitis and cirrhosis. There were significant differences between these two groups and the moderate/severe hepatitis group. CDT offers no additional benefit or greater differentiation than HVTT and can be omitted, thus simplifying this technique. HVTT may complement liver biopsy and may also be a useful alternative for assessment of liver disease in patients who have contraindications to biopsy.
Publication Types:
Evaluation Studies
PMID: 15591518 [PubMed - indexed for MEDLINE]

20: Hepatology. 2004 Dec;40(6):1426-33.
Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure.
Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, Moussalli J, Thabut D, Buffet C, Poynard T.
Service d'Hepato-Gastroenterologie, GH Pitie-Salpetriere, Paris, France. vdimartino@chu-besancon.fr
Female sex is a protective factor for the progression of fibrosis in patients with chronic hepatitis C virus (HCV) infection. Experimental data suggest that estrogens may have an antifibrotic effect. The objective of this study was to evaluate the influence of past pregnancies, oral contraceptives, menopause, and hormone replacement therapy (HRT) on liver fibrosis progression in HCV-infected women. Four hundred seventy-two HCV-infected women received a survey regarding prior pregnancies, menopause, and the use of oral contraceptives and HRT. The impact of these variables on liver fibrosis and its progression were evaluated using multivariate analyses considering all putative confounding factors. Two hundred one women completed the survey (43% response rate), 157 of whom had an
estimated date of HCV infection (96 postmenopausal women, 96 women with previous
pregnancies, and 105 women with past use of oral contraceptives). Through multivariate analyses, the estimated rate of fibrosis progression was higher in

postmenopausal (P < .05) and nulliparous (P = .02) women and was associated with greater histological activity (P < .001). Prior use of oral contraceptives had no significant influence. Among postmenopausal women, the estimated rate of fibrosis progression (+/-SE) was lower in women who received HRT compared with untreated patients (0.099 +/- 0.016 vs. 0.133 +/- 0.006 METAVIR units/yr; P = .02) and was similar to that of premenopausal women (0.093 +/- 0.012 METAVIR units/yr; P value not significant). In conclusion, menopause appears to be associated with accelerated liver fibrosis progression in HCV-infected women, an effect that may be prevented by HRT. Pregnancies may have a beneficial impact on the long-term progression of liver fibrosis.
PMID: 15565616 [PubMed - indexed for MEDLINE]

21: Hepatology. 2004 Dec;40(6):1450-8.
Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy.

Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, Wright TL, Mody SH, Tang KL, Goon BL, Bowers PJ, Leitz G, Afdhal NH; PROACTIVE Study Group.
Scripps Clinic, La Jolla, CA 92037, USA. ppockros@scrippsclinic.com
Anemia and decreased health-related quality of life (HRQL) are common in patients receiving combination therapy of interferon alfa (IFN) and ribavirin (RBV) for chronic hepatitis C virus (HCV) infection. In a randomized, prospective study evaluating the effectiveness of epoetin alfa in maintaining RBV dose, alleviating anemia, and improving HRQL in anemic (Hb < or = 12 g/dL) HCV-infected patients receiving combination therapy, patients receiving epoetin alfa had significant improvements in HRQL compared with placebo. In this study, 185 patients were randomized to 40,000 units of epoetin alfa subcutaneously weekly or placebo for an 8-week double-blind phase (DBP), followed by an 8-week open-label phase during which all patients received epoetin alfa. To further assess the impact of epoetin alfa on HRQL, post hoc analyses were conducted in the same patient population to compare the HRQL of these patients at randomization with norms of other populations, and to determine the critical relationship between hemoglobin (Hb) levels and HRQL. Mean HRQL scores of anemic HCV-infected patients receiving combination therapy at randomization were significantly lower than those of both the general population and patients who had other chronic conditions. Patients receiving epoetin alfa who had the greatest Hb increases from randomization to the end of the DBP also had the largest improvements in HRQL. Hb improvement was an independent predictor of HRQL improvement in these patients. In conclusion, epoetin alfa provided clinically significant HRQL improvement in HCV-infected patients receiving IFN/RBV therapy.
Publication Types:
Clinical Trial
Randomized Controlled Trial
PMID: 15565613 [PubMed - indexed for MEDLINE]

22: Hepatology. 2004 Dec;40(6):1434-41.
Chronic hepatitis C virus infection: does it really impact health-related quality of life? A study in rural Egypt.
Schwarzinger M, Dewedar S, Rekacewicz C, Abd Elaziz KM, Fontanet A, Carrat F, Mohamed MK.
INSERM U444, Faculte de Medecine Saint-Antoine, Paris, France.
schwarzi@u444.jussieu.fr
Previous Western studies showed a consistent and marked reduction in

health-related quality of life (HRQOL) in patients chronically infected with hepatitis C virus (HCV). However, these studies were conducted on patients whose knowledge of their serological status may have affected their HRQOL. This HRQOL survey conducted in the Egyptian rural population provides a unique opportunity to clarify this issue among a population whose serological status is unknown. HRQOL was assessed by an Arabic translation of the Short-Form 12, and a visual analog scale of the relative severity of one's health status. HCV chronic infection was defined by positive tests for anti-HCV antibody and HCV-RNA. HRQOL was compared according to HCV chronic infection status in linear mixed models adjusted for potential confounding factors, such as age, sex, education, and health care-related risk factors, and adjusted for interviewer as a random effect. One hundred forty-six Egyptians chronically infected with HCV had similar Short-Form 12 and visual analog scale scores, compared with 1,140 uninfected controls from the same rural community. In individuals chronically infected with HCV, serum aminotransferase levels did not correlate with HRQOL. In conclusion, this study did not find a significant reduction of HRQOL in patients chronically infected with HCV compared with uninfected, contemporaneous controls. This may be explained in part by a lower morbidity amongst patients chronically infected with HCV in rural Egypt and a higher morbidity amongst uninfected controls as compared with those of Western studies, as well as a lack of awareness of hepatitis C serological status.
PMID: 15565610 [PubMed - indexed for MEDLINE]

23: Hepatology. 2004 Dec;40(6):1442-9.
Viral kinetics during antiviral therapy in patients with chronic hepatitis C and persistently normal ALT levels.
Kronenberger B, Herrmann E, Micol F, von Wagner M, Zeuzem S.
Klinik fur Innere Medizin II, Universitatsklinikum des Saarlandes, Homburg/Saar, Germany.
The aim of the present study was to compare viral kinetics between patients with chronic hepatitis C and persistently normal alanine aminotransferase (ALT) levels and those with elevated ALT levels. Kinetic parameters were derived from nonlinear, least square fitting of serum hepatitis C virus RNA quantifications collected from patients with chronic hepatitis C and persistently normal (n = 20) and elevated (n = 19) ALT levels before and during treatment with 180 mug pegylated interferon alpha-2a once weekly plus daily ribavirin. Patients with chronic hepatitis C and persistently normal ALT levels showed a trend to lower pretreatment infected cell loss (delta) (P = .13) but no differences in efficacy of blocking virus production (epsilon) and infected cell loss during treatment (mdelta) compared with patients with elevated ALT levels. Differences were significant for epsilon (P = .02) and delta (P = .04) when applying updated "healthy" levels for ALT (0.75 times and 0.63 times upper limit of normal for male and female patients, respectively). A significant reduction of the kinetic parameters epsilon, delta, and mdelta was observed in patients with elevated gamma-glutamyltranspeptidase (GGT) levels compared with patients with normal GGT
levels (P = .02, P = .005, and P = .02, respectively). In conclusion, viral kinetics are similar in patients with chronic hepatitis C and persistently normal ALT levels and those with elevated ALT levels. However, in patients with elevated GGT levels, a major association with reduced efficacy of blocking virus production and lower infected cell loss was observed. These data show that virological response in patients with chronic hepatitis C is less associated with baseline ALT than with GGT levels.
Publication Types:
Clinical Trial

Clinical Trial, Phase III
Multicenter Study
Randomized Controlled Trial
PMID: 15565603 [PubMed - indexed for MEDLINE]

24: Hepatology. 2004 Dec;40(6):1249-51.
Comment on:
Hepatology. 2004 Dec;40(6):1260-5.
Tinkering and tailoring with HCV therapy: can we get away with less?
Zekry A, Patel K, Muir A, McHutchison JG.
Publication Types:
Comment
Editorial
Review
PMID: 15558725 [PubMed - indexed for MEDLINE]

25: Hepatology. 2004 Dec;40(6):1260-5.
Comment in:
Hepatology. 2004 Dec;40(6):1249-51.
Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study.
Dalgard O, Bjoro K, Hellum KB, Myrvang B, Ritland S, Skaug K, Raknerud N, Bell H.
Department of Medicine, Aker University Hospital, Oslo, Norway. odalgard@ulrik.uio.no
The aim of this study was to determine the efficacy of 14 weeks of treatment in patients infected with hepatitis C virus (HCV) genotype 2 or 3 who achieve early virological response (EVR). In a noncontrolled multicenter trial, 122 treatment-naive patients received 1.5 mug/kg pegylated interferon alfa-2b subcutaneously once weekly and 800 to 1,400 mg/d ribavirin based on body weight. Treatment was stopped at week 14 in patients with EVR, defined as undetectable HCV RNA at weeks 4 and 8. Patients without EVR were assigned to 24 weeks of treatment. The primary end point was sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after end of treatment. Among the 122 patients, 95 (78%) had EVR and received 14 weeks of treatment. The remaining 27 (22%) were treated for 24 weeks. SVR was obtained in 85 (90%) of 95 patients in the 14-week treatment group and 15 of (56%) 27 in the 24-week treatment group. Altogether, SVR was obtained in 100 of 122 patients (82%; 95% CI, 75%-89%). SVR after 14 weeks of treatment was achieved more frequently among genotype 3a patients with low viral load compared with high viral load (98% vs. 79%; P = .019). Logistic regression analysis showed that absence of bridging fibrosis/cirrhosis was the only independent predictor of SVR. In conclusion, patients with genotype 2 or 3 and EVR obtained a high SVR after 14 weeks of treatment. The results need to be confirmed in a randomized, controlled study before this treatment approach can be recommended, particularly for patients with genotype 3 and high viral load or severe fibrosis.
Publication Types:
Clinical Trial
Multicenter Study
PMID: 15558712 [PubMed - indexed for MEDLINE]

26: Infection. 2004 Dec;32(6):369-71.
HAART-prolonged life of HIV-infected patients should not be shortened by hepatitis C.
Horster S, Goebel FD.

Dept. of Infectious Diseases, Medical Policlinic, Ludwig Maximilian University Munich, Pettenkoferstr. 8a, D-80336 Munich, Germany.
As highly active antiretroviral treatment (HAART) prolongs the life of HIV-infected individuals and reduces mortality associated with opportunistic infections, liver diseases have become a major challenge in the management of these patients. up to 45% of deaths of persons with HIV are related to endstage liver disease, some of which might have been avoided with a less hesitant approach to hepatitis C treatment in the setting of HIV/ hepatitis C (HCV) coinfection.
PMID: 15597230 [PubMed - indexed for MEDLINE]

27: J Adolesc Health. 2004 Dec;35(6):505-8.
Seroprevalence of hepatitis C among a juvenile detention population.
Feldman GM, Sorvillo F, Cole B, Lawrence WA, Mares R.
Department of Public Health, County of Riverside, Riverside, California, USA.
The seroprevalence and determinants of hepatitis C virus (HCV) infection among adolescents in juvenile detention centers in Riverside County was assessed. Among 728 participants, 16 (2.2%, 95% CI 1.1%, 3.3%) demonstrated serologic evidence of HCV infection. Adolescents with a history of injection drug use (adjusted OR = 10.8, 95% CI 2.6, 45.3, P < .001) were more likely to be HCV seropositive, however the frequency of reported injection drug use was just 4%, and only 12% of HCV infection could be attributable to injecting drugs in this population. Additional information is needed on risk factors for HCV infection in adolescent populations. The relatively low level of HCV infection observed in this juvenile detention population underscores the opportunity for implementation of targeted intervention efforts.
PMID: 15581531 [PubMed - indexed for MEDLINE]

28: J Am Soc Nephrol. 2004 Dec;15(12):3249-55.
Hepatitis C, acute humoral rejection, and renal allograft survival.
Forman JP, Tolkoff-Rubin N, Pascual M, Lin J.
Department of Medicine, Brigham and Women's Hospital/Renal Division, 75 Francis Street, MRB-4, Boston, MA 02115, USA.
The effect of recipient hepatitis C virus (HCV) infection on renal allograft loss and acute rejection in kidney transplantation remains controversial. We studied 354 renal allograft recipients transplanted during 1996 to 2001 who had HCV antibodies (Ab) measured before transplantation. The primary outcome was death-censored allograft loss and the secondary outcome was acute humoral rejection (AHR). Compared with HCV Ab-negative patients, those with positive HCV Ab had longer time on dialysis before transplantation, higher percentage of panel-reactive antibodies (PRA), were more likely to receive a cadaveric transplant, and were more likely to develop delayed graft function (DGF). In univariate analyses, predictors of renal allograft loss included HCV, cadaveric graft, PRA >20%, HLA mismatch > or =5, retransplantation, DGF, induction therapy, and AHR. When adjusted for PRA >20%, HLA mismatch > or =5, and multiple
transplant status, HCV was not a statistically significant predictor of allograft loss. HCV was also associated with AHR but lost significance when adjusted for PRA >20%. HCV Ab-positive patients were more likely to have longer duration of dialysis before transplantation prior to kidney transplants, higher PRA, and to receive cadaveric transplants. These characteristics likely resulted in more DGF and AHR after transplantation. After adjusting for these confounding factors, the association between HCV Ab positivity and renal allograft loss was

notably attenuated and no longer statistically significant.
PMID: 15579529 [PubMed - indexed for MEDLINE]

29: J Am Soc Nephrol. 2004 Dec;15(12):3166-74.
Impact of diabetes and hepatitis after kidney transplantation on patients who are affected by hepatitis C virus.
Abbott KC, Lentine KL, Bucci JR, Agodoa LY, Koff JM, Holtzmuller KC, Schnitzler MA.
Nephrology Service, Walter Reed Army Medical Center, Washington, DC 20307-5001, USA. kevin.abbott@na.amedd.army.mil
Complications associated with use of donor hepatitis C-positive kidneys (DHCV+) have been attributed primarily to posttransplantation liver disease (as a result of hepatitis C disease). The role of posttransplantation diabetes has not been explored in this setting. With the use of the United States Renal Data System database, 28,942 Medicare KT recipients were studied from January 1, 1996, through July 31, 2000. Cox proportional hazards regression models were used to calculate adjusted hazard ratios (AHR) for the association of sero-pairs for HCV (D+/R-, D+/R+, D-/R+ and D-/R-) with Medicare claims for de novo posttransplantation HCV and posttransplantation diabetes. The peak risk for posttransplantation HCV was in the first 6 mo after transplantation. The incidence of posttransplantation HCV after transplantation was 9.1% in D+/R-, 6.3% in D+/R+, 2.4% in D-/R+, and 0.2% in D-/R-. The incidence of posttransplantation diabetes after transplantation also peaked early and was 43.8% in D+/R-, 46.6% in D+/R+, 32.3% in D-/R+, and 25.4% in D-/R-. Associations
for both complications were significant in adjusted analysis (Cox regression). Both posttransplantation HCV (AHR, 3.36; 95% confidence interval, 2.44 to 4.61) and posttransplantation diabetes (AHR, 1.81; 95% confidence interval, 1.54 to 2.11) were independently associated with an increased risk of death, but posttransplantation diabetes accounted for more years of life lost, particularly among recipients of DHCV+ kidneys. Posttransplantation diabetes may contribute substantially to the increased risk of death associated with use of DHCV+ kidneys and accounts for more years of life lost than posttransplantation HCV. Because HCV infection acquired after transplantation is so difficult to treat, methods that have been shown to reduce viral transmission warrant renewed attention.
PMID: 15579520 [PubMed - indexed for MEDLINE]

30: J Infect Dis. 2005 Jan 1;191(1):4-10. Epub 2004 Dec 02.
Comment in:
J Infect Dis. 2005 Jan 1;191(1):1-3.
Effect of hepatitis C virus (HCV) genotype on HCV and HIV-1 disease.
Yoo TW, Donfield S, Lail A, Lynn HS, Daar ES; Hemophilia Growth and Development Study.
Los Angeles Biomedical Research Institute at Harbor-University of California at Los Angeles Medical Center, Divisions of HIV Medicine and Infectious Diseases, Department of Medicine, David Geffen School of Medicine, CA 90502, USA.
The relationship between hepatitis C virus (HCV) genotype and HCV and human immunodeficiency virus (HIV) type 1 disease is not well defined. The present study analyzed data from a cohort of 207 HIV-1-infected and 126 HIV-1-uninfected children and adolescents with hemophilia who enrolled in the Hemophilia Growth and Development Study and were followed for 7 years. The mean HCV RNA level was higher in the participants in the HCV genotype 1 group than in the participants the HCV non-genotype 1 group, among both the HIV-1-infected (difference, +0.33 log(10) copies/mL; P=.038) and HIV-1-uninfected (difference, +0.59 log(10) copies/mL; P=.008) participants. Although HCV genotype was not associated with

differences in HIV-1 RNA level, a significantly lower mean CD4(+) T cell count (difference, -127 cells/ microL; P=.026) and percentage of CD4(+) T cells (difference, -4.3%; P=.027) were observed in the participants in the HCV genotype 1 group, compared with those in the participants in the HCV non-genotype 1 group. In addition, the participants in the HCV genotype 1 group were at increased risk for progression to AIDS-related mortality (hazard ratio, 2.44; P=.037). The present study suggests that HCV infection and genotype may influence the natural history of HCV and HIV-1 disease.
PMID: 15592996 [PubMed - indexed for MEDLINE]

31: J Infect Dis. 2005 Jan 1;191(1):1-3. Epub 2004 Dec 02.
Comment on:
J Infect Dis. 2005 Jan 1;191(1):4-10.
Hepatitis C virus (HCV) genotypes and disease progression in HIV/HCV-coinfected patients.
Nunez M, Soriano V.
Publication Types:
Comment
Editorial
PMID: 15592995 [PubMed - indexed for MEDLINE]

32: J Intern Med. 2004 Dec;256(6):529-30; author reply 531.
Comment on:
J Intern Med. 2004 Mar;255(3):399-408.

A reappraisal of the Barcelona Clinic Liver Cancer model: natural history of untreated 'intermediate stage' hepatocellular carcinoma.
Farinati F, Marino D, De Giorgio M, Trevisani F.
Publication Types:
Comment
Letter
Multicenter Study
PMID: 15554955 [PubMed - indexed for MEDLINE]

33: J Med Virol. 2005 Feb;75(2):258-66.
Molecular investigation of interspousal transmission of hepatitis C virus in two Japanese patients who acquired acute hepatitis C after 40 or 42 years of marriage.
Nakayama H, Sugai Y, Ikeya S, Inoue J, Nishizawa T, Okamoto H.
Department of Internal Medicine, Iwaki Kyoritsu General Hospital, Fukushima-Ken, Japan.
A 65-year-old woman (C1I) and a 65-year-old man (C2I) contracted acute hepatitis C 40 or 42 years after marriage, respectively, in Japan. They had no discernible risk factors for acquiring hepatitis C virus (HCV) infection, except that they had monogamous sexual relationships with their spouses (C1S [66-year-old] with hepatocellular carcinoma and C2S [64-year-old] with liver cirrhosis, respectively) who were infected with HCV of the same genotype (1b) and had a high-titer HCV RNA in the serum (bDNA probe assay, 17 Meq/ml [C1S] and 15 Meq/ml
[C2S]). The HCV isolates from Patients C1I and C1S and those from Patients C2I and C2S shared identity of 99.9% and 99.1%, respectively, in the 1,087-nucleotide (nt) sequence of the NS5B region, although these four isolates were only 91.7%-96.2% identical to the 94 reported genotype 1b isolates including those from Japanese patients. To confirm the high degree of genetic relatedness among ten HCV clones from each spouse within each pair of spouses, the E1 and E2 junctional region sequence (268 or 271 nt) including hypervariable

region 1 (HVR-1) was analyzed. There was a close relationship between clones obtained from each spouse within each couple. Regarding the HVR-1 amino acid sequence, nine of the ten C1I clones were 100% identical with six of the ten C1S clones, and one each of the C2I and C2S clones differed by only one amino acid residue. This study indicates that two Japanese patients with acute hepatitis C had acquired HCV infection most probably by interspousal sexual transmission during a long-lasting marriage.
Publication Types:
Case Reports
PMID: 15602741 [PubMed - indexed for MEDLINE]

34: J Med Virol. 2005 Feb;75(2):209-12.
HCV and HIV co-infection in pregnant women attending St. Camille Medical Centre in Ouagadougou (Burkina Faso).
Simpore J, Ilboudo D, Samandoulougou A, Guardo P, Castronovo P, Musumeci S.
Laboratoire Saint Camille de Ouagadougou, Burkina Faso, Unite de Formation et de Recherche/SVT, Universite de Ouagadougou, Ouagadougou, Burkina Faso.
Five hundred and forty-seven pregnant women with less than 32 weeks of amenorrhoea, attending an antenatal clinic of St. Camille Medical Centre (SCMC) of Ouagadougou were enrolled for a hepatitis C virus (HCV) and HIV co-infection study. Fifty-eight (10.6%) were HIV positive and 18 (3.3%) were anti-HCV positive. Only seven pregnant women (i.e., 1.3%) had a documented HIV and HCV co-infection. HCV-RNA was found in 5 out of 18 (27.8%) patients, who had anti-HCV antibodies. The genotype analysis of these five patients showed that two were of 1b whereas three were of 2a genotype. Mother-to-infant transmission of the same HCV genotype (2a) was documented in only one case. High 1b prevalence has been reported in other parts of Africa, while 2a is the prevalent genotype (60%) in Burkina Faso. This genotype has a higher response rate to treatment. Serum transaminases were normal, also in presence of HCV-RNA. The higher than expected rate of co-infection in Burkina Faso seems to demonstrate a correlation between these two infections, which could influence the evolution of HIV and HCV diseases.
PMID: 15602740 [PubMed - indexed for MEDLINE]

35: J Med Virol. 2005 Feb;75(2):222-6.
Liver histology in patients with HBsAg negative anti-HBc and anti-HCV positive chronic hepatitis.
Sagnelli E, Pasquale G, Coppola N, Marrocco C, Scarano F, Imparato M, Sagnelli C, Scolastico C, Piccinino F.
Department of Public Medicine, Division of Infectious Diseases, Second University of Naples, San Sebastiano Hospital, Caserta, Italy. evangelista.sagnelli@unina2.it
The liver histology of 68 consecutive anti-HCV/HCV-RNA positive chronic hepatitis patients who were HBsAg/anti-HBs negative, anti-HBc positive (Case bC group) was compared with that of 68 anti-HCV/HCV-RNA positive chronic hepatitis patients who were HBsAg/anti-HBc negative (control C group). The patients were pair-matched by age (+/-5 years), sex, and risk factors for the acquisition of parenteral infection. Case bC group showed a significantly higher mean fibrosis score (2.3 +/- 1.1) than control C group (1.5 +/- 1.1, P <0.001) and more histological evidence of cirrhosis (22% vs. 7.3%, P <0.05). In addition, the patients in Case bC group showed more severe inflammation of the portal tracts (3.5 +/- 0.8 vs. 3.0 +/- 1.1, P <0.005) and there was a higher prevalence of patients with rhomboid-shaped hepatocytes (26.4% vs. 2.7%, P <0.005), acidophilic bodies (33.8% vs. 1.4%, P <0.0001), sinusoidal inflammation (29.4% vs. 10.3%, P <0.01), lymphoid follicles in the portal tracts (72% vs. 44.1%, P

<0.05), Kupffer cell proliferation (29.4% vs. 11.8%, P <0.05), bile duct damage (44.1% vs. 10.3%, P <0.0001), and ductular proliferation (30.9% vs. 2.7%, P <0.001) than in control C group. No difference in these histological features was observed between HBV-DNA negative and positive patients in Case bC group. The data suggest that anti-HBc positive patients with HCV chronic infection have a significantly higher degree of liver fibrosis, and that hepatocellular apoptosis, bile duct damage, and ductular proliferation correlate with the presence of this antibody in the serum.
PMID: 15602732 [PubMed - indexed for MEDLINE]

36: J Med Virol. 2005 Feb;75(2):240-8.
Clinical and virological characteristics of untreated patients with chronic hepatitis C who develop serum alanine aminotransferase flare-up.
Hiraga N, Suzuki F, Akuta N, Suzuki Y, Sezaki H, Hosaka T, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Matsuda M, Watabiki S, Satoh J, Kumada H.
Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan.

Among patients with chronic hepatitis C virus (HCV) infection, serum alanine aminotransferase (ALT) rarely increases above 500 IU/L. We examined the clinical and virological features of untreated patients with serum ALT > or = 500 IU/L. One thousand seven hundred and sixty adult patients with chronic HCV infection were followed-up. Among these patients, 22 developed ALT flare-up (M:F=13:9, median age, 50.5 years). We evaluated liver function tests, genotype, and viral titer in these patients and 44 randomly selected age- and sex-matched control without ALT flare-up. In four patients with ALT flare-up, we examined changes in viral loads and sequential changes in amino acid sequences of the core region, hypervariable region 1 (HVR1), and interferon sensitivity determining region (ISDR) before and after ALT flare-up. Multivariate analysis identified genotype 2 as the only significant determinant of ALT flare-up. ALT flare-up occurred in three of four patients without increase in viral load. Several alterations in amino acids were noted in HVR1 before and within 6 months of ALT flare-up. One or two alterations in the core region and many alterations in HVR1 were noted after ALT flare-up in some patients. Genotype 2 is an important factor for ALT flare-up. However, we could not directly relate ALT flare-up to these alterations in amino acids of the core region, HVR1, and ISDR.
PMID: 15602722 [PubMed - indexed for MEDLINE]

37: J Sch Nurs. 2004 Dec;20(6):324-30.
Bloodborne infections: should they be disclosed? Is differential treatment necessary?
Kukka C.
Parents of Kids with Infectious Diseases (PKIDs), Scarborough, ME, USA.
There are students and staff in many schools with hepatitis B, hepatitis C, or HIV infections. Should parents or guardians be expected to disclose students' bloodborne infections to school officials? Can infected students play contact sports given the increased risk of blood spills? What type of response plan should schools develop in the event of a blood spill to protect student health and privacy? This article summarizes the policies and approaches that the federal government and medical, school nursing, teacher, and parent organizations have taken on these issues. It suggests strategies school nurses can employ to protect the civil rights, privacy, and health of all students and school staff.
Publication Types:
Review
Review, Tutorial
PMID: 15560729 [PubMed - indexed for MEDLINE]

38: J Virol. 2005 Feb;79(3):1569-80.
Hepatitis C virus (HCV) constitutively activates STAT-3 via oxidative stress: role of STAT-3 in HCV replication.
Waris G, Turkson J, Hassanein T, Siddiqui A.
Department of Microbiology and Program in Molecular Biology, University of Colorado HSC, 4200 East Ninth Ave., Denver, CO 80262, USA.
The hepatitis C virus (HCV) causes chronic hepatitis, which often results in liver cirrhosis and hepatocellular carcinoma. We have previously shown that HCV nonstructural proteins induce activation of STAT-3 via oxidative stress and Ca2+ signaling (G. Gong, G. Waris, R. Tanveer, and A. Siddiqui, Proc. Natl. Acad. Sci. USA 98:9599-9604, 2001). In this study, we focus on the signaling pathway leading to STAT-3 activation in response to oxidative stress induced by HCV translation and replication activities. Here, we demonstrate the constitutive activation of STAT-3 in HCV replicon-expressing cells. The HCV-induced STAT-3 activation was inhibited in the presence of antioxidant (pyrrolidine dithiocarbamate) and Ca2+ chelators (BAPTA-AM and TMB-8). Previous studies have shown that maximum STAT-3 transactivation requires Ser727 phosphorylation in addition to tyrosine phosphorylation. Using a series of inhibitors and dominant negative mutants, we show that HCV-induced activation of STAT-3 is mediated by oxidative stress and influenced by the activation of cellular kinases, including p38 mitogen-activated protein kinase, JNK, JAK-2, and Src. Our results also suggest a potential role of STAT-3 in HCV RNA replication. We also observed the constitutive activation of STAT-3 in the liver biopsy of an HCV-infected patient. These studies provide an insight into the mechanisms by which HCV induces intracellular events relevant to liver pathogenesis associated with the viral infection.
PMID: 15650183 [PubMed - indexed for MEDLINE]

39: J Virol. 2004 Dec;78(24):13591-9.
Molecular characterization of human immunodeficiency virus type 1 and hepatitis C virus in paid blood donors and injection drug users in china.
Zhang L, Chen Z, Cao Y, Yu J, Li G, Yu W, Yin N, Mei S, Li L, Balfe P, He T, Ba L, Zhang F, Lin HH, Yuen MF, Lai CL, Ho DD.
Aaron Diamond AIDS Research Center, The Rockefeller University, 455 First Ave., 7th Floor, New York, NY 10016, USA. lzhang@adarc.org.
China is facing a rapid upsurge in cases of human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) infection due to large numbers of paid blood donors (PBD), injection drug users (IDU), and sexual partners of infected individuals. In this report, a total of 236 HIV-1-positive blood samples were collected from PBD, IDU, and their sexual partners in the most severely affected provinces, such as Henan, Yunnan, Guangxi, and Xinjiang. PCR was used to amplify the p17 region of gag and the C2-V3 region of env of HIV-1 and the 5' noncoding region and a region of E1/E2 of HCV. Genetic characterization of viral sequences indicated that there are two major epidemics of HIV-1 and multiple HCV epidemics in China. The PBD and transfusion recipients in Henan harbored HIV-1 subtype B', which is similar to the virus found in Thailand, and HCV genotypes 1b and 2a, whereas the IDU in Yunnan, Guangxi, and Xinjiang carried HIV-1 circulating recombinant forms 07 and 08, which resemble those in India, and HCV genotypes 1b, 3a, and 3b. Our findings show that the epidemics of HIV-1 and HCV infection in China are the consequences of multiple introductions. The distinct distribution patterns of both the HIV-1 and HCV genotypes in the different high-risk groups are tightly linked to the mode of transmission rather than geographic proximity. These findings provide information relevant to antiviral therapy and vaccine development in

China and should assist public health workers in implementing measures to reduce the further dissemination of these viruses in the world's most populous nation.
PMID: 15564470 [PubMed - indexed for MEDLINE]

40: JAMA. 2004 Dec 15;292(23):2909-13.
Comment on:
JAMA. 2004 Dec 15;292(23):2839-48.
Treatment of hepatitis C in HIV-infected patients: significant progress but not the final step.
Manns MP, Wedemeyer H.
Publication Types:
Comment
Editorial
PMID: 15598923 [PubMed - indexed for MEDLINE]

41: JAMA. 2004 Dec 15;292(23):2839-48.
Comment in:
JAMA. 2004 Dec 15;292(23):2909-13.
Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial.
Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, Morand P, Goujard C, Pialoux G, Piroth L, Salmon-Ceron D, Degott C, Cacoub P, Perronne C; ANRS HCO2 RIBAVIC Study Team.
Groupe Hospitalier Universitaire Est, Universite Paris 6, INSERM U444, Paris, France.
CONTEXT: Treatment of chronic hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)-infected patients is a growing concern. Most data on the virologic efficacy and safety of the combination of peginterferon alfa-2b and ribavirin in coinfected patients come from uncontrolled studies. OBJECTIVE: To study the safety and efficacy of peginterferon alfa-2b plus ribavirin vs standard interferon alfa-2b plus ribavirin in HIV-HCV coinfected patients. DESIGN AND SETTINGS: A multicenter, randomized, parallel-group, open-label trial. Patients were enrolled from February 2000 to February 2002 and followed up for 72 weeks. PATIENTS: Four hundred twelve HIV-HCV coinfected patients with detectable serum HCV-RNA, abnormal liver histology, a CD4 cell count of at least 200 x 10(6)/L, and stable plasma HIV-RNA. INTERVENTION: Treatment with ribavirin 400 mg twice a day, orally, plus either peginterferon alfa-2b (1.5 microg/kg subcutaneous injection once a week) or standard interferon alfa-2b (3 million units of subcutaneous injection 3 times a week) for 48 weeks. MAIN OUTCOME MEASURES: Sustained virologic response, defined by undetectable serum HCV-RNA at
week 72. RESULTS: More patients had sustained virologic responses in the peginterferon group than in the standard interferon group (27% vs 20%, P = .047). This difference between the treatments was found in patients with HCV genotype 1 or 4 infection (17% for peginterferon vs 6% for standard interferon, P = .006) but was not found in patients with HCV genotype 2, 3, or 5 (44% for peginterferon vs 43% for standard interferon, P = .88). Together, a decline in HCV-RNA of less than 2 log10 from baseline and detectable serum HCV-RNA at week 12 predicted 99% of treatment failures. Histologic activity diminished and fibrosis stabilized in virologic responders. The 2 regimens showed similar tolerability although dose modifications for clinical and biological events were more frequent with peginterferon. Eleven cases of pancreatitis or symptomatic hyperlactatemia were observed, all in patients receiving didanosine-containing

antiretroviral regimens. CONCLUSION: In combination with ribavirin, treatment with peginterferon alfa-2b is more effective than standard interferon alfa-2b for HCV infection in HIV-infected patients.
Publication Types:
Clinical Trial
Clinical Trial, Phase III
Multicenter Study
Randomized Controlled Trial
PMID: 15598915 [PubMed - indexed for MEDLINE]

42: Lancet. 2005 Jan 22;365(9456):327-9.
Comment in:
Lancet. 2005 Jan 22;365(9456):276-8.
T-cell responses and previous exposure to hepatitis C virus in indeterminate blood donors.

Semmo N, Barnes E, Taylor C, Kurtz J, Harcourt G, Smith N, Klenerman P.
Peter Medawar Building for Pathogen Research, University of Oxford, Oxford, UK.
Blood donors are routinely screened for hepatitis C virus infection. Some individuals have weak or restricted virus-specific antibody responses, and are classed as indeterminate. Such donors are almost always negative for viral RNA in blood. We postulated that previous transient virus exposure might account for some of these cases. With sensitive ex-vivo analyses of T-cell responses, we identified virus-specific responses in 15 of 30 indeterminate blood donors tested, compared with none in controls (p=0.0013). Additionally, these responses were typically focused on core-derived peptides. These findings suggest previous exposure to the virus in many indeterminate blood donors.
PMID: 15664228 [PubMed - indexed for MEDLINE]

43: Lancet. 2005 Jan 22;365(9456):276-8.
Comment on:
Lancet. 2005 Jan 22;365(9456):327-9.
Hepatitis C virus in blood donation.
Allain JP.
Division of Transfusion Medicine, Department of Haematology, University of Cambridge, Cambridge CB2 2PT, UK. Jpa1000@cam.ac.uk
Publication Types:
Comment
PMID: 15664206 [PubMed - indexed for MEDLINE]

44: Laryngoscope. 2004 Dec;114(12):2119-22.
Prevalence and epidemiology of hepatitis C virus in patients with squamous cell carcinoma of the head and neck.
Nobles J, Wold C, Fazekas-May M, Gilbert J, Friedlander PL.
Department of Otolaryngology and Biocommunication, Hematology and Oncology Division, Louisiana State University Health Sciences Center-New Orleans, 533 Bolivar Street, New Orleans, LA 70112, U.S.A.
OBJECTIVE: Recently, we have noticed that a large number of patients with squamous cell carcinoma of the head and neck (SCCHN) are also infected with the hepatitis C virus (HCV). A review of the literature has revealed no published studies examining this association. The objective of this study was to determine the incidence and epidemiology of HCV infection in patients with SCCHN. STUDY DESIGN: A retrospective chart review. METHODS: Patients diagnosed with SCCHN were analyzed to determine whether they were screened for HCV. Patients were then stratified into two groups (HCV positive and HCV negative). The patient's

age at onset, site and stage of the tumor at presentation were determined, and statistical analysis was performed. RESULTS: Ninety-nine (26%) patients were screened, and 21 (21.2%) were HCV positive. This incidence was increased when compared with previously published data (9.9%) (P < .0038). HCV-positive patients presented at an earlier age (51 years) versus the HCV-negative group (60 years) (P < .0002). There were no significant differences in the site or stage at presentation. CONCLUSIONS: In this study, 21% of patients diagnosed with SCCHN were found to be infected with HCV. These patients presented at an earlier age but had similar presentation with respect to site and stage. More research is needed to determine the significance of HCV infection in this patient population.
PMID: 15564831 [PubMed - indexed for MEDLINE]

45: Metab Brain Dis. 2004 Dec;19(3-4):421-9.
Fatigue complicating chronic liver disease.
Jones EA.
Department of Gastrointestinal and Liver Diseases, Academic Medical Center, 1105 AZ Amsterdam-ZO, The Netherlands. tjones@xs4all.nl
Fatigue is common and can be profound in patients with chronic liver diseases, such as primary biliary cirrhosis (PBC) and chronic hepatitis C. The pathogenesis of fatigue in such patients is unknown; it may be related to infection with the hepatitis C virus or the pathophysiology of cholestasis in PBC, to a psychological reaction to knowledge of the diagnosis, or to the presence of chronic liver disease. A major problem in evaluating a treatment for fatigue in a randomized controlled trial is the inherent subjectivity of fatigue and the lack of a satisfactory objective quantitative primary efficacy endpoint. Experimental studies in rats and male athletes have implicated the serotonin neurotransmitter system in fatigue of central origin. Administration of the 5-HT3 serotonin receptor subtype antagonist, ondansetron, has been associated with substantial sustained clinical ameliorations of profound fatigue in at least some patients with chronic liver disease.
Publication Types:
Review
PMID: 15554432 [PubMed - indexed for MEDLINE]

46: Metab Brain Dis. 2004 Dec;19(3-4):383-91.
Central nervous system involvement in hepatitis C virus infection.
Forton DM, Thomas HC, Taylor-Robinson SD.
Hepatology Section, Division of Medicine A, Faculty of Medicine, Imperial College, London, United Kingdom. d.forton@imperial.ac.uk
Hepatic encephalopathy is the most obvious neurological consequence of chronic hepatitis C virus (HCV) infection. There are also case reports of HCV-associated cerebral vasculitis. This review is concerned with the possibility of an effect of HCV on cerebral dysfunction, occurring at an early stage of chronic infection, prior to the development of cirrhosis and unrelated to vasculitis. There is emerging evidence of mild, but significant neurocognitive impairment in HCV infection, which cannot be attributed to substance abuse, coexistent depression, or hepatic encephalopathy. In vivo magnetic resonance spectroscopy and neurophysiological studies have suggested that a biological mechanism may underlie these cognitive findings. The recent detection of HCV genetic sequences in postmortem brain tissue raises the intriguing possibility that HCV infection of the central nervous system may be related to the reported neuropsychological symptoms and cognitive impairment.
Publication Types:

Review
PMID: 15554429 [PubMed - indexed for MEDLINE]

47: Metab Brain Dis. 2004 Dec;19(3-4):357-81.
Hepatitis C virus-associated extrahepatic manifestations: a review.
Sene D, Limal N, Cacoub P.
Department of Internal Medicine, Boulevard de l'hopital, Paris, France.
The hepatitis C virus (HCV) infection is a worldwide disease that is characterized by a preferential chronic evolution with mild to severe liver disease, including cirrhosis and, in lesser proportion, hepatocarcinoma. Out of these complications, HCV is frequently reported to complicate extrahepatic manifestations. Among those associated to HCV infection with a high degree of certainty, mixed cryoglobulinemia and its complications (skin, neurological, renal, rheumatological involvement) are the most prevalent (50%) in HCV-infected patients. The other diseases include noncryoglobulinemic systemic vasculitis, splenic lymphoma with villous lymphocytes, fatigue, porphyria cutanea tarda, sicca syndrome, and autoantibodies production. The extrahepatic manifestations that share mild-degree certainty of association with HCV infection include B-cell non-Hodgkin lymphoma, autoimmune thrombocytopenia, pruritus, and type II diabetes mellitus. The other diseases such as autoimmune thyroiditis, lichen planus are more questionable for their eventual association with HCV and others (pulmonary fibrosis with or without polymyositis, progressive encephalomyelitis, Mooren's corneal ulcers, erythema nodosum, chronic polyradiculonevritis) are mostly case reports. Howerver, even in cases of tight association, the mechanisms through which HCV may promote or induce extrahepatic manifestations remain unclear and merit further investigations.
Publication Types:
Review
PMID: 15554428 [PubMed - indexed for MEDLINE]

48: Metab Brain Dis. 2004 Dec;19(3-4):351-6.
Hepatitis C virus infection and the brain.
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While HCV was initially believed to uniformly cause liver inflammation with the consequence of liver cirrhosis in most of the infected patients, prospective studies have shown a much lower than expected rate of cirrhosis in patients infected for more than 20 years. However, a new problem associated with hepatitis C virus infection is emerging. This is the development of sometimes disabling fatigue. While many other viruses of the flaviviridae cause encephalitis, the most closely related virus to HCV in humans, the GB Virus C seems not to be associated with fatigue. Thus the mechanism for the development of fatigue in HCV infection seems specific for HCV. Delineating the mechanism will be a first step to develop treatment option for this currently untreatable impairment.
Publication Types:
Review
Review, Tutorial
PMID: 15554427 [PubMed - indexed for MEDLINE]

49: Nature. 2004 Dec 16;432(7019):922-4.
Modelling how ribavirin improves interferon response rates in hepatitis C virus infection.
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Nearly 200 million individuals worldwide are currently infected with hepatitis C virus (HCV). Combination therapy with pegylated interferon and ribavirin, the latest treatment for HCV infection, elicits long-term responses in only about 50% of patients treated. No effective alternative treatments exist for non-responders. Consequently, significant efforts are continuing to maximize response to combination therapy. However, rational therapy optimization is
precluded by the poor understanding of the mechanism(s) of ribavirin action against HCV. Ribavirin alone induces either a transient early decline or no decrease in HCV viral load, but in combination with interferon it significantly improves long-term response rates. Here we present a model of HCV dynamics in which, on the basis of growing evidence, we assume that ribavirin decreases HCV infectivity in an infected individual in a dose-dependent manner. The model
quantitatively predicts long-term response rates to interferon monotherapy and combination therapy, fits observed patterns of HCV RNA decline in patients undergoing therapy, reconciles conflicting observations of the influence of ribavirin on HCV RNA decline, provides key insights into the mechanism of ribavirin action against HCV, and establishes a framework for rational therapy optimization.
PMID: 15602565 [PubMed - indexed for MEDLINE]

50: Nature. 2004 Dec 2;432(7017):540.
Canada pledges cash for more victims of blood-bank debacle.
Spurgeon D.
Publication Types:
News
PMID: 15577872 [PubMed - indexed for MEDLINE]

51: Rom J Gastroenterol. 2004 Dec;13(4):329-32.
HCV carriers with persistently normal ALT Levels: not too much healthy, not true patients.
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Approximately 30% of patients with chronic HCV infection show persistently normal alaninaminotransferase (ALT) levels. The majority of HCV carriers are females, and up to 40-50% of carriers harbor non-1 genotype, at least in western Europe. No association has been found between HCV type/viral load and the severity of liver damage. The prevalence of HCV carriers with normal liver seems to be very low (less than 20%). Liver disease is usually minimal/mild and fibrosis is generally absent or minimal, although the association of normal ALT
with cirrhosis or with hepatocellular carcinoma has been reported. In all studies, liver histology was, on average, significantly less severe in subjects with persistently normal ALT than with abnormal ALT. Although the majority of data seem to show that HCV carriers with normal ALT have mild and stable disease, with a favourable prognosis, several studies reported a significant
progression of fibrosis in approximately 20-30% of the patients with ALT normality, and the development of hepatocellular carcinoma in some cases has been described, despite persistent ALT normality. Sudden worsening of disease with ALT increase and histological deterioration has been described after up to 15 years of follow-up.
Publication Types:
Review
Review, Tutorial
PMID: 15624031 [PubMed - indexed for MEDLINE]

52: Rom J Gastroenterol. 2004 Dec;13(4):317-27.
Living donor liver transplantation and hepatitis C.
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Preliminary results indicate that living donor liver transplantation (LDLT) recipients infected with HCV develop earlier and more severe recurrence than their cadaveric counterparts. The mechanisms underlying this observation are unknown, but could include hepatic regeneration, differences in LDLT recipient demographics, immune homology between donor and recipient, or other factors not previously considered. The optimum clinical approach is to consider LDLT in HCV-infected recipients only as a life-saving procedure and to attempt to eradicate HCV before LT to prevent recurrent infection.
Publication Types:
Review
Review, Tutorial
PMID: 15624030 [PubMed - indexed for MEDLINE]

53: Rom J Gastroenterol. 2004 Dec;13(4):291-7.
Progression of liver fibrosis in blood donors infected with hepatitis C virus.
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BACKGROUND/AIMS: Chronic hepatitis by HCV is progressive towards cirrhosis, with variable rate. We evaluated the rate of fibrosis progression (RFP), risk factors associated with advanced fibrosis (F3 and F4), and estimated the evolution time to cirrhosis. METHODS: We transversely selected 142 blood donors infected only with HCV, with a known route of infection, submitted to liver biopsy at admission. RFP= ratio between stage of fibrosis (METAVIR)/estimated duration of infection in years. Non-parametric tests and logistic regression analysis, with significance level of 5% were used. RESULTS: Median RFP was 0.086 U/year (0.05-0.142). Ten patients had F4 and 25 had F3. Median RFP values were significantly different (p=0.001) from one age group at contamination to the others and ALT and AST levels. There were no differences in the expected evolution to cirrhosis between intermediate fibrosers (F2) and the rapid fibrosers (F3 and F4). The independent variables associated with advanced fibrosis were ALT (OR 7.2) and GGT (OR 6.4) and age at inclusion (OR 1.12). CONCLUSION: This study suggests that RFP is extremely variable, it is exponential with age, and mainly influenced by host characteristics, especially age at contamination and possibly ethnical group. These asymptomatic patients had high percentage of fibrosis F2, F3 and F4.
PMID: 15624026 [PubMed - indexed for MEDLINE]

54: Toxicol Lett. 2005 Jan 15;155(1):171-7.
Comparison of cytochrome P4502E1 (CYP2E1) activity and hepatic and lymphocyte mRNA expression in patients with chronic hepatitis C.
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The induction of cytochrome P4502E1 (CYP2E1) is believed to play a role in the

development of fibrosis in hepatitis C patients. However, information about CYP2E1 activity in chronic hepatitis C patients is fragmentary and the relationship between CYP2E1 activity and mRNA expression is unknown in this disease. The purpose of this study was (a) to characterise CYP2E1 activity in those patients and (b) to analyse its relationship with CYP2E1 mRNA expression in the liver and in peripheral blood lymphocytes (PBLs), previously proposed as a surrogate to assess changes in CYP2E1 activity. Fourteen chronic hepatitis C patients were submitted to a routine transcutaneous liver biopsy. CYP2E1 activity was assessed by using chlorzoxazone (CZX) pharmacokinetic parameters and hepatic and PBLs CYP2E1 mRNA expression was measured by real-time RT-PCR. The mean oral clearance of CZX (CLT: 21.5+/-10.1L/h) was within the normal range and the chlorzoxazone metabolic ratio (CMR) at t = 2 h was closely related to other CZX pharmacokinetic parameters. None of the pharmacokinetic parameters did significantly correlate with CYP2E1 mRNA, neither in the liver nor in PBLs. Furthermore, there was no significant relationship between CYP2E1 mRNA levels in paired liver and PBL samples. Our data indicate that early stages of chronic hepatitis C are not associated with CYP2E1 induction. In this disease, the determination of the CMR at t = 2 h represents a reliable index to assess CYP2E1 activity. The measurement of CYP2E1 expression, at the mRNA level, in PBLs or in liver is not useful for that purpose.
PMID: 15585372 [PubMed - indexed for MEDLINE]

55: Transfusion. 2004 Dec;44(12):1706-10.
The hepatitis C virus genotype and subtype frequency in hepatitis C virus RNA-positive, hepatitis C virus antibody-negative blood donors identified in the nucleic acid test screening program in Poland.
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BACKGROUND: Since 2002, blood donors in Poland have been tested not only for hepatitis C virus antibodies (anti-HCV) but also for HCV RNA or HCV core antigen. This screening program identifies asymptomatic, recently infected individuals with no anti-HCV (in the "window period"). The aim of this study was to compare HCV genotype and subtype distribution in window-period (wp) donors, anti-HCV-positive donors, and chronic hepatitis C (CHC) patients. STUDY DESIGN AND METHODS: A total of 2.37 million donors were investigated for HCV RNA, and 340,000 for HCV core antigen. HCV genotypes and subtypes were investigated in 50 HCV RNA-positive, anti-HCV-negative donors; in 70 anti-HCV-positive donors; and in 170 CHC patients. Re-questioning of wp donors for probable risk factors was introduced. RESULTS: HCV RNA was detected in 50 donors of 2.71 million (1:54,200) anti-HCV-negative blood donations. Of these 50 donors, 36 percent exhibited Subtype 1b, whereas Subtypes 3a and 4c/d were identified in 40 and 14 percent, respectively. In anti-HCV-positive donors and CHC patients, the frequency of Subtype 1b was significantly higher (75.7 and 85.3%, respectively); in both groups the lower frequency of Subtypes 3a (14.3 and 10.6%, respectively) and 4c/d (4.3 and 1.2%, respectively) was found. The probable source of infection was identified in 9 wp donors. CONCLUSIONS: The frequency of wp donors is 18.5 per 1 million. The unexpected high frequency of Genotype 4 and Subtype 3a and the low frequency of Subtype 1b was observed in wp donors compared to anti-HCV-positive individuals. Additional epidemiologic questioning introduced after HCV RNA detection may help to identify infection source.
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